## Remarks

Claims 23-26, 28-34 are pending. Claims 28 and 31-32 are cancelled. Claims 29, 30 and 34 are currently amended. The amendments are merely for the sake of clarity. Claims 23-26, 29-30 and 33-34 (formerly identified as Claims 31-32) are rejected. This is consistent with the identification of the rejected claims in the Official Action and the renumbering of the claims discussed below.

The Applicants thank the Examiner for the withdrawal of all the rejections in the final Official Action dated June 25, 2008.

An objection has been made to the numbering of the claims. The Applicants wish to clarify that previously pending Claims 31-32 had withdrawn status and are now cancelled. Additionally, the new claims entered in the Response dated January 25, 2008 have been renumbered as Claims 33 and 34. The Applicants respectfully submit that the pending claims are now numbered correctly.

The Applicants respectfully request the withdrawal of the objections to the claims.

Claims 29-30 are rejected under 35 USC §112, second paragraph, as indefinite.

Amended Claims 29-30 are definite under 35 USC §112, second paragraph. The amended claims no long recite "analog[s]" and now recite "pharmaceutically acceptable salts[.]" Sufficient antecedent basis for "pharmaceutically acceptable salts" can be found in independent Claim 23 on which amended Claims 29 and 30 depend.

The Applicants respectfully request the withdrawal of the rejections of Claims 29-30 under 35 USC §112, second paragraph.

Claims 23-26, 29, 33 and 34 are rejected as anticipated under 35 USC §102(b) by de Vos. The Applicants note that Claims 31 and 32 identified in the rejection are now identified as Claims 33 and 34.

Claims 23-26, 29, 33 and 34 are not anticipated under 35 USC §102(b) by de Vos. de Vos fails to teach all the elements of independent Claim 23 which recites a "pharmaceutically acceptable agent" and requires "an amount [of the claimed compositions] sufficient to induce analgesia and/or deter abuse of abusive substances."

Those of ordinary skill in the art would understand a "pharmaceutically acceptable agent" to mean carriers, excipients, fillers *etc.* that do not adversely affect drug compounds or patients.

Human blood plasma is not a "pharmaceutically acceptable agent[.]" There are several reasons for this.

First, it should be noted that human blood plasma is simply a blood cell-free fluid fraction prepared from whole human blood. Human blood plasma is by no means sterile or otherwise free of infectious agents such as viruses, bacteria, fungi, protozoan parasites (*e.g.*, malaria causing plasmodium parasites) and prions capable of causing serious harm to patients. Second, it is well known in the art that human blood plasma is not biologically inert or inactive. Instead, human blood plasma is biologically active and contains enzymes which are capable of reacting with, and degrading, drug compounds. Human blood plasma also contains hormones, immunoglobulins (*e.g.*, antibodies), cytokines and other molecules, including drugs and toxins in some instances, which can cause serious adverse reactions in patients and adversely affect the stability of drug compounds. Altogether, this means that human blood plasma is not a "pharmaceutically acceptable agent."

Additionally, de Vos does not teach an amount of EDDP or any of the other compounds of the claims sufficient to "induce analgesia and/or deter abuse of abusive substances." This is not surprising considering that de Vos is merely concerned with developing a chromatographic technique "to investigate the pharmacokinetics of methadone and its primary metabolite EDDP in 20 long-term opiate addicts." *See* de Vos at 364. In fact, de Vos acknowledges previous studies found "no analgesic activity for EDDP" and fails to provide any experimental data showing EDDP, or the other compounds of the claims, have analgesic activity or can deter the abuse of abusive substances. *See* de Vos at 364 (emphasis added).

Altogether, this means that de Vos fails to teach all the elements of independent Claim 23 or Claims 24-26, 29, 31 and 34 which depend on this claim.

The Applicants respectfully request the withdrawal of the rejections of Claims 23-26, 29, 33 and 34 under 35 USC §102(b).

Claim 30 is rejected as obvious under 35 USC §103(a) over de Vos.

Amended Claim 30 is not obvious under 35 USC §103(a) over de Vos.

First, as discussed above, de Vos fails to teach all the elements of amended Claim 30 because it does not teach a "pharmaceutically acceptable agent" or "an amount [of the claimed compositions] sufficient to induce analgesia and/or deter abuse of abusive substances."

Second, the Applicants respectfully note that, over the three decades preceding the Applicants' invention, it remained settled in the prior art that EDDP and the other compounds of the claims, such as EDDP derived salts, had no analgesic activity. In fact, in 1971 Pohland explicitly states that "[m]etabolites III [(EDDP)] and VI [(an EDDP derived salt)] are inactive in pharmacological tests" and thus teaches away from the claimed pharmaceutical compositions. *See* Pohland at 194 and 197. Pohland also provides extensive experimental data in the art accepted rat tail jerk model supporting this teaching and states that "the two metabolites of methadone [(compounds III, EDDP, and VI, an EDDP derived salt)] do not elicit agonist or antagonist properties when tested" and did not antagonize the analgesic effects of methadone or morphine in this model. Furthermore, as discussed above, de Vos acknowledges previous studies found "no analgesic activity for EDDP[.]" *See* de Vos at 364 (emphasis added). Thus, the Applicants respectfully request that all the teachings of the prior art, including those teachings that explicitly teach away from the claimed pharmaceutical compositions, be considered.

Third, one of ordinary skill in the art would not be motivated to modify de Vos to arrive at the claimed pharmaceutical compositions. This is because, when all the teachings of the prior art are considered, the prior art explicitly, and consistently, taught that EDDP and the other compounds of the claims have no analgesic activity. *See e.g.*, Pohland (discussed above). Importantly, de Vos failed to conduct a single experiment investigating the ability of EDDP, or any of the other compounds of the claims, to "induce analgesia and/or deter abuse of abusive substances." This is significant because it seems that, at a minimum, such data would be necessary to make one of ordinary skill in the art disregard the fact that, despite three decades of related research and publications, it remained settled in the prior art that EDDP and the other compounds of the claims had no analgesic activity. The Applicants also again note the prior art appears to be silent concerning the use of such compounds in deterring the abuse of abusive substances. This means EDDP and the other compounds of the claims were, until the Applicants' invention, long acknowledged in the art and by de Vos itself as being pharmacologically inactive. Consequently, the Applicants respectfully submit that, on consideration of all the teachings of the prior art, one of ordinary skill in the art would not be motivated to modify the disclosure of de Vos to arrive at the claimed pharmaceutical compositions or reasonably expect success on so doing.

Altogether, the above discussion makes it clear the rejection fails to establish *prima facie* obviousness over de Vos.

The Applicants respectfully request the withdrawal of the rejection of Claim 30 under 35 USC §103(a) based on de Vos.

Claims 23-26, 29-30 and 33-34 are rejected as obvious under 35 USC §103(a) over the combination of Pohland and Gunaratna. The Applicants note that Claims 31 and 32 identified in the rejection are now identified as Claims 33 and 34.

Claims 23-26, 29-30 and 33-34 are not obvious under 35 USC §103(a) over the combination of Pohland and Gunaratna. First, as discussed above, Pohland teaches by way of experimental data generated in an art accepted model that "metabolites III [(EDDP)] and VI [(an EDDP derived salt)] are inactive in pharmacological tests[,]" that "the two metabolites of methadone [(compounds III, EDDP, and VI, an EDDP derived salt)] do not elicit agonist or antagonist properties when tested[,]" and that these compounds did not antagonize the analgesic effects of methadone or morphine in this model. Thus, one of ordinary skill in the art would not be motivated to modify the teachings of Pohland because Pohland teaches that EDDP is not biologically active. Stated differently, Pohland explicitly teaches away from the combination suggested by the rejection.

Second, Pohland fails to teach all the elements of the claimed pharmaceutical compositions. This is because Pohland does not teach a pharmaceutically acceptable agent in combination with EDDP, or the other compounds of the claims. In fact, Pohland is entirely silent regarding the use of a pharmaceutically acceptable agent with EDDP or an EDDP derived salt and may simply have administered the crystalline solid forms of these compounds alone to the patients. Furthermore, neither Pohland nor Gunaratna teaches an amount of a pharmaceutical composition containing these compounds "sufficient to induce analgesia and/or deter abuse of abusive substances." Thus, the combination of Pohland and Gunaratna fails to teach all the elements of the claimed pharmaceutical compositions.

Third, the teachings in Pohland render the teachings of Gunaratna regarding drug metabolism and pharmacokinetic studies irrelevant. This is because one of ordinary skill in the art would have absolutely no motivation to engage in such studies or modification of a xenobiotic compound with no known biological activity. This exact situation is presented here,

because Pohland teaches that EDDP and the other compounds of the claims lack analgesic activity and does not teach these compounds can prevent the abuse of an abusive substance.

This means that one of ordinary skill in the art would understand from Gunaratna, in view of the teachings of Pohland, that the situation resulting from methadone administration is best described by the scenario in Fig. 4 of Gunaratna. In this scenario, a drug produces an inactive metabolite without pharmacological activity. Importantly, Gunaratna provides no rationale relating to this scenario that would motivate one of ordinary skill in the art to pursue such a pharmacological dead end. This means, one of ordinary skill in the art would not be motivated to combine Pohland and Gunaratna to arrive at the claimed pharmaceutical compositions as suggested in the rejection nor reasonably expect success on so doing.

Altogether, the above discussion makes it clear the rejection fails to establish *prima facie* obviousness over the combination of Pohland and Gunaratna.

The Applicants respectfully request the withdrawal of the rejections of Claims 23-26, 29-30 and 33-34 under 35 USC §103(a).

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

T. Daniel Christenbury
Reg. No. 31,750
Attorney for Applicants

TDC/vbm
(215) 656-3381